Focus

Extra Ingredients: Hormones in Food

The endocrine system produces hormones that play crucial roles in reproduction, development, and metabolism. However, fish, wildlife, and humans consume food and water containing environmental toxicants that behave like hormones and have the ability to cause effects, sometimes irreversible, ranging from sterility and abnormal sex differentiation to cancer. Pregnant women exposed to these substances can transfer the effects to their fetuses.

Consensus is building in favor of public policies to control or eliminate these suspect compounds that exist as environmental contaminants or food additives and to encourage much-needed further research. However, these efforts have met with some resistance. According to the National Agricultural Chemicals Association (NACA), some alleged associations between environmental estrogenic compounds and health risks "have been blown out of proportion," said John McCarthy, NACA's vice president for global scientific and regulatory affairs. Because several of these products are no longer used, he said, the problems they may have caused are subsiding.

Nat'l. Agricultral Chem. Association

John McCarthy—Health risks of environmental estrogens have been blown out of proportion.

Naturally Occurring Hormones

Certain plant foods, notably legumes, contain hormonelike substances called phytoestrogens that may protect against disease as well as cause harm. On the down side, one class of plant estrogens, isoflavonoids, seem to have an adverse influence on sexual development. When researchers fed female rats a diet containing the isoflavonoid coumestrol, the female offspring manifested early and irregular menstrual cycles. The male offspring did not gain weight as fast as the controls before puberty; they also "showed deficits in mating behavior," reported Patricia L. Whitten, biologic anthropologist at Emory University in Atlanta. All the offspring obtained the coumestrol from mother's milk. Whitten's experiments suggest that coumestrol may act on more targets than just estrogen receptors—perhaps at the level of the central nervous system, for instance—and thereby may have a variety of indirect effects that contribute to its estrogenic action. Another experiment showed that coumestrol induces uterine growth, as opposed to an increase in weight due to water influx, demonstrating that estrogen activity occurs, Whitten explained.

Whitten points out that sheep that graze on isoflavonoid-rich pasture for prolonged periods develop an infertility syndrome known as "clover disease," and cattle have similar reactions. Another plant estrogen, zearalenone, a product of the *Fusarium* fungus which commonly infests corn in storage, reportedly caused sterility and other reproductive defects in livestock fed moldy grain.

On the positive side, it appears that phytoestrogens might guard against breast cancer. Phytoestrogens appear in high concentrations in the urine of Asian women, who have very low rates of breast cancer, but are found in low concentrations in the urine of breast cancer patients. Donna D. Baird, an epidemiologist at NIEHS, led a study in which postmenopausal women were fed a soy diet to see if it induced the same biological changes that take place in women on replacement estrogen therapy. The soy diet did not produce similar changes, though there was evidence of vaginal cell changes as a result of estrogens. Unfortunately, said Baird, "it is hard to conclude anything broad because the women only ate the diet for four weeks. Maybe if they ate it for eight weeks, things would change. Maybe soybeans aren't particularly effective."

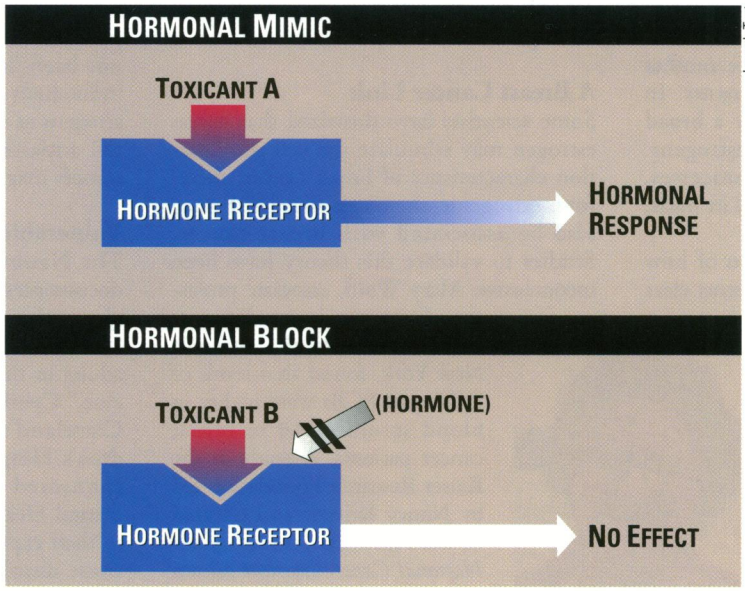
The Bettman Archive

Mooore milk. Although the FDA has approved use of bovine growth hormone to increase milk production, many consumers and some scienists wonder if it's worth the potential genetic price.

Hormone Additives

Food additives always seem to stir up safety debates, and hormone additives are no exception. One recent debate centers around recombinant bovine growth hormone, also known as bovine somatotropin (BST), which is injected into cows to increase their milk output. The FDA approved the genetically engineered hormone on 5 November 1993, and Monsanto, the sole producer, is selling its product under the brand name Posilac.

Consumer activists oppose BST because treated cows tend to suffer from mastitis, an udder infection which requires antibiotic therapy. The activists contend that the drug encourages multiplication of antibiotic-resistance genes that are passed to humans, making it difficult or impossible to treat many diseases. The antibiotic-resistance genes have been found in meat, especially meat that is undercooked or raw, and in fruits and vegetables fertilized with manure from treated cows, according to physician Jeffrey A. Fisher, author of *The Plague Makers.*



Joseph Tart

Under lock and key. Environmental hormones can cause problems when they interfere with normal hormone receptor sites.

Another concern is IGF-1, a growth factor and an intermediary by which BST acts. "It is the same as human IGF-1, and there are elevated levels of it in cows and milk. It could affect the tissues it touches in the colon, to cause colon cancer," said Jean Halloren of the Consumers Union, the nonprofit consumer testing and advocacy organization that publishes *Consumer Reports*. "This is a biologically powerful substance. It needs close attention, but has not gotten close attention," Halloren said. Others such as Samuel E. Epstein, professor of occupational and environmental medicine at the University of Illinois at Chicago, have warned about possible breast cancer from the increased IGF-1 levels due to BST.

The FDA refutes both the Consumer Union's and Epstein's views. Citing studies demonstrating BST does not increase the IGF-1 content, the agency issued a statement explaining: "The IGF-1 content that occurs naturally in human breast milk occurs at about the same concentration as that found in cow's milk. Levels of IGF-1 in cows' milk and meat are very much lower than the levels found naturally in human blood and other body tissues. IGF-1 is not absorbed intact. Dietary IGF-1 in milk and meat is broken down in the gastrointestinal tract by digestion. Undigested IGF is excreted."

Even so, Epstein's claim that IGF-1 increases the growth of breast cells in culture has given many scientists something to think about, though what happens in culture and what happens in the human body could be very different. Some scientists say there is no evidence that the increase in breast cells leads to malignancy, as Epstein asserts. Although the activists failed to convince the FDA to ban BST, they did persuade major dairy producers as well as supermarket chains not to use BST or to sell dairy products from treated cows.

Hormone Impersonators

Several environmental chemicals mimic or interfere with female and male hormones, thereby impairing reproduction and growth. One of the first major breakthroughs was the discovery of vaginal cancer and other problems in sex organs of daughters of women who received DES (diethylstilbestrol), a drug prescribed to prevent spontaneous abortions, from 1948 to 1971. Laboratory experiments demonstrated these same effects in female animals and others in male animals. Later, human studies unearthed comparable effects in the sons of DES-exposed mothers.

"We recreated animal models for both sons and daughters that were enormously predictive of effects in humans," said John McLachlan of NIEHS. "We discovered while doing that work that DES also was being given to cattle as a growth-promoting substance. So we started to think about estrogenic materials in the environment because it was estimated some 13 tons of DES was added every year to the environment through feedlots and feedlot wastes." DES has since been outlawed for use in animals.

Meanwhile, scientists were finding events in nature that resembled those induced by DES. An early sign that environmental chemicals might impair endocrine function was the discovery in the 1950s that DDT caused birds such as sea gulls and bald eagles to lay eggs with thin shells, with the result that many embryos were crushed to death. In addition, reproduction in gull colonies heavily exposed to DDT began to decline precipitously in the late 1960s, apparently because in some cases two females, instead of a male and female, were sharing nests, and the young in the communities had grossly feminized reproductive organs.

Similar situations have come to light over the years. In the 1980s, D. Michael Fry of the University of California-Davis reported of wild birds: "Organic chlorine chemicals build up in the yolk of eggs and result in testes which have both ovarian and testicular regions, so that the birds are essentially intersex and chemically sterile." Louis J. Guillette, Jr., a reproductive endocrinologist at the University of Florida in Gainesville, uncovered permanent damage to the reproductive system of DDT-contaminated alligators in Lake Apopka. In the Great Lakes, sexual aberrations and unstable populations among 16 major species have been related to the presence of estrogenic chemicals such as PCBs, DDT, and its metabolites. Humans eating Great Lakes fish have experienced comparable problems. Women who ate two to three Lake Michigan fish a month for at least six years preceding their pregnancies bore children who were slightly preterm, had lower birth weight, smaller skull size, and a number of other deficits compared with babies of mothers who did not eat fish. The children were examined at age four, and those whose mothers had eaten contaminated fish exhibited short-term memory problems.

Whitten examined several human historical trends such as reduction in the age of first intercourse, increase in the incidence of sexual intercourse, and the disappearance of sex differences in coital behavior, plus declines in the age of menarche and in fraternal twinning, and concluded the data "suggest that some fundamental shifts in the human reproductive development have occurred over the last century . . . [and] coincide with changes in diet and chemical production, both of which have the potential to influence developmental processes."

Another sign that environmental hormones may adversely affect sexual development is the decline in sperm counts and semen volume in men over the past 50 years. In one study of 14,947 men, sperm count dropped by almost 50% between 1940 and 1990, and the amount of semen the men were able to produce dropped an average of almost 20%. Estrogenic compounds loom as a major problem. They include the organohalogen pesticide DDT and its major metabolite, DDE, which accumulate in body fat and are found in breast milk; hydroxylated forms of polychlorinated biphenyls (PCBs), used as pesticides and in electrical components, which also accumulate in body fat and have been found in fish; *p*-nonyl-phenol and bisphenol-A, which are released from some plastics under various conditions. Bisphenol-A is also involved in detergent manufacturing

and has been linked to feminization of fish species in England.

Dioxins and dibenzofurans are another group of hormonelike contaminants. In laboratory animals, they modify a broad array of hormones, including estrogens. Waste products of industrial processes, these chemicals have been found in meat, dairy products, and fish oil.

In the still-unfolding scenario of how endocrine disruptions occur, it seems clear that an environmental chemical can connect itself to the same receptor sites to which a natural hormone attaches to turn on a message. Normally, this lock-and-key mechanism controls the way the embryo develops from inception through birth as well as the cascade of events that follow through life. A critical stage is the point at which the embryo develops male or female characteristics and the testes, ovaries, and related traits are defined. One environmental insult at that sensitive time may cause abnormalities. For example, chemicals with vastly different structures can activate the same estrogen receptor, causing estrogen-type responses, which in turn could account for reproductive abnormalities. In contrast, some chemicals can block the receptor system, preventing estrogen from binding to its receptors. Scientists are researching the complex signaling pathways by which environmental hormones function. "We now know molecules that look so different can act the same because there may be other molecules that are activated, like growth factors," said McLachlan.

EPA

Penelope Fenner-Crisp—Effects attributed to hormones may result from hormone blocking.

Some environmental compounds resemble male hormones. One example is vinclozolin, a fungicide used on fruits and vegetables, which interferes with the performance of male sex hormones. When a pregnant rat is exposed to high doses of vinclozolin during embryonic development, males are born without a penis or with other malformations of sex organs. The mechanism by which vinclozolin acts is unclear. Feminization could occur because something has disturbed the masculinization rather than increased estrogen, explained Penelope A. Fenner-Crisp, director of the health effects division of EPA's Office of Pesticide Program. "One complicating factor," she said, "is if you just run an animal study and do not measure hormones or don't measure receptor binding, but you see either behavior, anatomical, or functional changes that reflect reproductive disturbances, you could interpret an effect as attributable to estrogen when, in fact, it could be attributable to having blocked the androgen."

A Breast Cancer Link

Some scientists have theorized that excess estrogen may stimulate the cell proliferation characteristics of breast cancer; therefore, estrogenic chemicals like DDE may also be associated with breast cancer. Studies to validate this theory have been inconclusive. Mary Wolff, associate professor of community medicine at Mt. Sinai Medical Center in New York, found that levels of DDE and PCBs were higher in blood serum of 58 in breast cancer patients. A study at the Kaiser Research Foundation led by Nancy Krieger and released in the April 20 *Journal of the National Cancer Institute* refutes Wolff's findings. "Our results do not support the hypothesis that DDE and PCBs are a risk factor for breast cancer," wrote the researchers. Wolff said, "You have to look more closely at the data and see that in blacks and whites, there is definitely a dose-related increase in breast cancer, although they don't achieve statistical significance. But the numbers are small. We consider them consistent with our earlier data."

The Kaiser team expressed concern about lack of adequate data on lactation, which is the chief route by which women excrete organochlorines. A relationship between lactation and DDT levels was reported in the 1970s when Walter Rogan of NIEHS led a study that examined 858 children from birth to one year old to determine whether the presence of PCBs or DDE in breast milk affected their growth or health. Though the children had no apparent health problems, the ones whose mothers had higher blood levels of DDE were breast fed for markedly shorter times. "We speculate that DDE may be interfering with the mother's ability to lactate, possibly because of its estrogenic properties," reported the researchers. A comparable outcome resulted from a study of Mexican women in a cotton-growing region where DDT levels are high.

Stephen Safe of the Department of Veterinary Physiology and Pharmacology at Texas A&M University points out that in some studies dioxins at certain levels inhibited cancer cell proliferation. These antiestrogen properties "are great if you are a woman with breast cancer," he said. "But 90% of women do not get breast cancer, and an antiestrogen would not be good for them." Safe notes that the whole question of hazardous environmental hormones is complex and controversial. "Some bizarre positions have been taken, and they have not been balanced," he said. Given that individuals consume estrogens and antiestrogens as well as weak estrogens and partial antiestrogens, some of these circumstances may counteract each other.

Vulnerable Youngsters

The National Academy of Sciences has documented children's special susceptibility to the toxic effects of chemicals. "Children cannot be considered little adults in the area of environmental medicine," Cynthia Bearer, a neonatologist with Cleveland's Rainbow Babies and Children's Hospital, told a recent conference sponsored by the Children's Environmental Health Network. Youngsters differ in their exposures, pathways of absorption, tissue distribution, ability to biotransform and eliminate chemicals, and response of tissues and organs to environmental chemicals and radiation. Differences depend on the developmental stage of the child.

Young people consume more milk fat and certain foods than adults, and a breast-fed child's exposure to hormonal contaminants such as dioxins, PCBs, and DDT can be 40 times greater than an adult's. It has been estimated that at least 5% of the babies born in the United States are exposed to quantities of PCBs sufficient to cause neurological effects. The irony is that while human milk is the major source of infant DDT exposure in the United States, lactation is the most efficient means of reducing a woman's body burden of organochlorines.

The vulnerability of children has been verified by several studies. In the mid-1980s, Puerto Rican girls who had consumed DES in meat developed large breasts at an early age and had other signs of precocious puberty. In Taiwan in 1979, a mass poisoning from PCB-contaminated rice bran oil had serious repercussions in children born to women who ate the rice. In 1985, 117 children born to women who had consumed contaminated oil and 118 unexposed controls were examined. The exposed children were shorter and weighed less; had more frequent abnormalities of the gums, skin, nails, teeth, and lungs; showed delays of developmental milestones, deficits on formal developmental testing, and abnormalities on behavioral assessment; and exposed boys at ages 11 to 14 had shorter penises. In the Netherlands, studies of healthy breast-fed infants showed those with higher concentrations of dioxins had higher concentrations of thyroid hormone, presumably because dioxins interfere with the thyroid hormone regulatory system (see Pluim et al., *EHP* 101: 504–509).

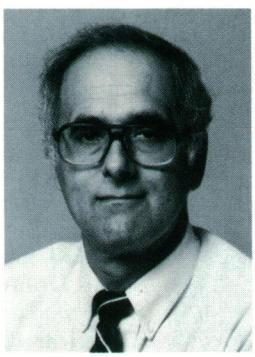
Exposure: How and How Much

Although individual exposures to all chemicals vary with socioeconomic, nutritional, and health status, everyone is exposed to a certain, perhaps dangerous, level of environmental hormones. Environmental hormones infiltrate food and water in places remote from the site of original release because chemicals are carried as particulates or gases in the air, surface waters, groundwater, and ocean currents across or between continents. Contaminated animals also travel great distances. Many environmental hormones accumulate in animal fat, becoming progressively concentrated in animals high up in the food chain. For instance, salmon eaten by humans may contain relatively high amounts of PCBs or dioxins in its body fat.

Many chemicals persist in the environment. "PCBs will be around for geologic time," predicts Theodora Colborn, a zoologist with the World Wildlife Fund. PCBs were introduced in the United States in 1929, and production ceased in 1972. But often the chemicals were not stored properly and were dispersed in the environment. DDT was applied on a large scale in the 1940s, and restrictions were put in place in 1972. But it is made abroad and used extensively in developing countries with limited safeguards. At one time, 15 chemicals similar to DDT and PCBs were registered in the United States; now there are 4, but only 1, endosulfan, has a number of food uses.

The EPA has been attempting to assess dioxin emission rates from hospital waste incinerators, industrial processes such as paper and pulp manufacture, forests fires and wood burning, diesel vehicles, and municipal waste incinerators and to measure background exposure in soil, air, and food. According to Linda S. Birnbaum, director of EPA's Health Effects Research Laboratory, breast-fed infants and subsistence fishermen are among groups with higher exposures than the average. "There are many other exposures from environmental hormones that the agency has not done as thorough a collection or analysis of," says John Schaum, environmental engineer in the EPA Office of Research and Development. "It is something we would like to do, but it is a matter of funding priorities. We would like to know levels in the physical environment and in foods."

Whitten proposes that dietary phytoestrogens be considered when making estimates of the total estrogenic load on humans. For example, "The presence of soy in a variety of processed foods from diet beverages to baby formulas provides a widespread source of exposure to these plant chemicals," she said. She also suggests lower estrogen exposure might result from diets containing lots of meat but little vegetable protein.



Texas A&M University

Stephen Safe—The issue of environmental hormones is complex and controversial.

Stemming the Tide

Colborn, a leading proponent of regulating toxic chemicals that have developmental influences, was instrumental in organizing two scientific conferences, one in 1991 and another in 1993, which produced consensus statements that environmental hormones pose serious threats to wildlife and human reproduction and that certain corrective measures should be undertaken. The 1993 report described "profound" threats to the survival of species from sexual disruptions and recommended that chemicals be tested before environmental release throughout a minimum of two generations for reproductive, immunological, endocrinological, and neurological effects. The report also called for awareness to be raised among legislators, scientists, public health officials, and the general public about the dangers of endocrine-disrupting chemicals and for a major research effort and comprehensive assessment of wildlife declines and diseases caused by chemicals on a global basis to be undertaken.

In calling for premarket screening of estrogenic chemicals, the scientists urged development of cost-effective tests that do not use a lot of animals. McLachlan has recommended one possible approach called "functional toxicology," in which *in vitro* assays are used to learn the function of a compound (rather than its chemistry). McLachlan explained, "We have the biotechnological tools to put genes for many different receptors into human cells, so you don't have to worry about animals and making extrapolations. Then, we can screen chemicals to see if they work like an estrogen, androgen, retinoid, neurotransmitter, and so on. If they do, we learn something about the function of this chemical and the things it could do." In the same way Ames test helps screen for mutagenicity, McLachlan foresees functional toxicology assays enabling public health decisions regarding estrogenicity.

The NACA says the current approach works well enough. If a chemical caused estrogen disruption, McCarthy said, it would be seen in the lifetime feeding studies and developmental testing now performed. "We believe that using the whole animal and looking at all the reproductive functions is a much better model than testing outside of the animal with some enzymes and seeing whether or not it is estrogenic. . . . You still would have to go to the whole animal."

Consumer advocates fault the EPA's current method of assessing pesticide safety because it fails to address cumulative risk. The agency does not know which pesticides are used on particular foods, and it does not physically test all the combinations of pesticides to which a person may be exposed. Congressman Henry Waxman (D-California) has introduced an amendment to the Food Drug and Cosmetic Act (HR 4091) that requires the EPA to establish protocols "to determine whether a pesticide disrupts the endocrine systems, is neurotoxic, or reproductively or developmentally toxic," and to "mandate the relevant data."

The EPA says it has some knowledge of cumulative exposure. As Fenner-Crisp explained: "When we grant a use, we do a risk assessment on that use. If it happens to be a dietary use, we look at any other use that has been approved to that point. If this is the 13th use, we do a dietary risk assessment that includes the other 12. And, because of additional data we have generated, . . . we can get a better sense of what the real exposure is to a single chemical from all its pesticide use on food." However, she said, "we really don't know the extent to which anyone is being bombarded with chemicals that disturb hormonal balance."

Regulatory agencies are often forced to look at chemicals in isolation. However, many chemicals have competing or exacerbating actions, many of which have not been identified. Hormones also have widely varying activities within different cell types; for example, some chemicals may function like estrogen in breast cells but are antiestrogenic in liver cells. All of these factors make it difficult to assess the overall impact on human health from exposure to environmental hormones.

Goody L. Solomon

Goody L. Solomon is a freelance writer in Washington, DC.